

Amendment and Response*Serial No.: 09/772,598**Confirmation No.: 2967**Filed: January 30, 2001**For: CRYSTALLIZATION AND STRUCTURE DETERMINATION OF STAPHYLOCOCCUS AUREUS NAD SYNTHETASE*

*Page 8 of 15***Remarks**

The Office Action mailed October 1, 2002, has been received and reviewed. Claims 1-34, 36 and 37 having been canceled, and claims 35 and 38 having been amended, the pending claims are claims 35 and 38-43. Reconsideration and withdrawal of the rejections are respectfully requested.

The specification has been amended at pages 10-11 to format the line spacing of Tables 3-5 at 1.5 spaces per line. The specification has also been amended at page 26, line 9, to delete an unintentional recitation of a hyperlink. Finally, the specification has been amended at page 44, line 33 to correct a typographical error. The specification as amended correctly states that, excluding the N-terminal methionine, there are *four* methionines in each molecule. The amendment is supported, for example, by Figure 9 and the sequence listing (e.g., SEQ ID NO:1).

Claims 35 and 38 have been amended to further clarify the claims and to define abbreviations, which are also defined in the specification at, for example, page 12, line 11 to page 13, line 4.

Objection to Disclosure

The Examiner objected to the disclosure for containing an embedded hyperlink. The disclosure has been amended by deleting the unintentional recitation of a hyperlink, and the objection is obviated.

The Examiner also objected to the line spacing on pages 10-11, Tables 3-5. The specification has been amended at pages 10-11 to format the line spacing of Tables 3-5 at 1.5 spaces per line, and the objection is obviated.

Applicants respectfully request that the Examiner withdraw the objection to the specification.

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Objection to Claims

The Examiner objected to claims 35-38 for utilizing abbreviations, alleging that the use of abbreviations in claims is improper. Applicants respectfully traverse the objection. Claims 36 and 37 have been cancelled, rendering the objection moot with respect to those claims.

"[T]he terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description." 37 C.F.R. §1.75(d)(1). Thus, Applicants respectfully submit that the rules do not preclude the use of abbreviations in claims. Moreover, the M.P.E.P. even anticipates the use of abbreviations in claims ("Periods may not be used elsewhere in the claims except for abbreviations." M.P.E.P. §608.01(m)).

The Examiner objected to the use of the abbreviations PEG, DMSO, *S. aureus*, and NAD. Applicants respectfully submit that the meanings of these abbreviations are clear to one of skill in the art. Furthermore, the abbreviations are all defined in the specification at, for example, page 12, line 11 to page 13, line 4.

However, in the interest of expediting the prosecution of the present application, claims 35 and 38 have been amended to incorporate the unabbreviated form at the first occurrence of each abbreviation in each claim. In view of the remarks offered herein, Applicants respectfully request that the objection to the claims be reconsidered and withdrawn.

Rejections under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 35-37 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner stated that the phrase "molecular complex" is vague and indefinite. Applicants respectfully traverse the rejection. Claims 36 and 37 have been canceled, rendering the rejection moot with respect to those claims.

Applicants respectfully submit that the phrase "molecular complex" is clear and definite when read in view of the specification at, for example, page 25, lines 24-25. However,

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in the interest of expediting the prosecution of the present application, claim 35 has been amended to delete the recitation of "molecular complex, " and the rejection is obviated.

Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §112, First Paragraph***ENABLEMENT***

The Examiner rejected claims 35-43 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner alleged that Applicants have failed to indicate suitable conditions for the crystallization of *Staphylococcus aureus* nicotinamide adenine dinucleotide. The Examiner states that "[p]roper disclosure for the conditions for crystallization (i.e., pH, concentration of protein, reagents, etc) is required for enablement" (page 4, lines 15-17 of the Office Action mailed October 1, 2002). Applicants respectfully traverse the rejection. Claims 36 and 37 have been canceled, rendering the rejection moot with respect to those claims.

Claim 35, as amended, recites:

35. A method for crystallizing *Staphylococcus aureus* nicotinamide adenine dinucleotide (*S. aureus* NAD) synthetase comprising:
providing purified *S. aureus* NAD synthetase at a concentration of about 1 mg/ml to about 50 mg/ml; and
crystallizing *S. aureus* NAD synthetase from a solution comprising about 5% by weight to about 50% by weight polyethylene glycol (PEG) and about 0% by weight to about 20% by weight dimethyl sulfoxide (DMSO).

This embodiment of the method of the invention is explicitly set forth in the specification at page 9, lines 8-13. Moreover, although not required, the specification includes a working example (Example I) that directly supports the claimed method by describing

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crystallization of *S. aureus* NAD synthetase using 15% PEG 1500 (page 41, lines 10-11), 16-22% PEG (page 41, lines 20-21) and 18-22% PEG (page 42, lines 6-7). Crystallization conditions were described, and certainly they are "suitable" as they led to the formation of crystals. The fact that, in detailing the crystallization process, the Applicants also set forth factors discovered during optimization that made crystallization more difficult does not mean that "suitable conditions" were not described. Furthermore, although crystallization conditions using PEG without salt or additional PH control were found to be preferred, it should also be noted that crystallization "hits" were observed under conditions that included pH control and ammonium sulfate, in addition to PEG (specification at page 41, lines 7-9).

Claims 38-43 are directed to a crystal of *S. aureus* NAD synthetase. Applicants submit that, in enabling claim 35, drawn to a method for making a crystal of *S. aureus* NAD synthetase, claims directed to the crystal (claims 38-43) are likewise enabled.

Applicants therefore respectfully submit that the claimed subject matter is described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

WRITTEN DESCRIPTION

The Examiner also rejected claim 43 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention. Specifically, the Examiner alleged that SEQ ID NO:1 includes numerous methionines, that the specification fails to indicate which methionine(s) (by position) are replaced (individually and/or in combination), and that one of skill in the art would at least expect such replacement to result in structurally different coordinates. Applicants respectfully traverse the rejection.

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Claim 43 recites a crystal of *Staphylococcus aureus* nicotinamide adenine dinucleotide (*S. aureus* NAD) synthetase having amino acid sequence SEQ ID NO:1, with the proviso that at least one methionine is replaced with selenomethionine. Applicants note that SEQ ID NO:1 includes an N-terminal methionine (residue 1) and four non-terminal methionines (e.g., residues 13, 26, 64, and 143). Although not required, Applicants have provided a working example of a crystal of *S. aureus* NAD synthetase having amino acid sequence SEQ ID NO:1, with the proviso that at least one methionine is replaced with selenomethionine (e.g., specification at, for example, page 40, lines 3-19; page 42, lines 23-25; page 43, line 24 to page 45, line 8; and page 47, lines 1-5). The specification (as amended) characterizes the selenomethionine enriched material by stating, for example, that "[t]here are four methionines in each molecule of NadE excluding the N-terminal methionine. Therefore, the eight [selenium] heavy atom positions would be consistent with the presence of two molecules in the asymmetric unit" (page 44, line 33 to page 45, line 2). Thus, the specification characterizes the selenomethionine enrichment at any or all of the four non-terminal methionines. Based on the arguments presented herein, Applicants respectfully submit that the specification reasonably conveys to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention.

Moreover, Applicants respectfully disagree with the Examiner's assertion that one of skill in the art would at least expect such replacement to result in structurally different coordinates. First, replacement of methionine by selenomethionine is well known in the art of protein crystallography as a method of incorporating heavy atoms into a molecule to aid in the solution of the x-ray crystal structure for the native molecule (e.g., without selenomethionine). The technique is useful *specifically* because the incorporation of the heavy atoms does not substantially disrupt the crystal structure. *See, for example*, Hendrickson et al., "Selenomethionyl proteins produced for analysis by multiwavelength anomalous diffraction (MAD): a vehicle for direct determination of three-dimensional structure," *EMBO J.*, 9:1665-1672 (1990) (listed on a 1449 form included in the Information Disclosure Statement submitted herewith). Furthermore, the intent of the Examiner's statement that one of skill in the art would

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at least expect such replacement to result in structurally different coordinates is unclear, as claim 43 does not recite specific structure coordinates. Clarification is respectfully requested in the next Official Communication.

Based on the remarks presented herein above, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §102

The Examiner rejected claims 35-40 under 35 U.S.C. §102(b) as allegedly being anticipated by Rizzi et al. ("Crystallization of NAD⁺ Synthetase from *Bacillus subtilis*," *Proteins: Structure, Function, and Genetics*. 1996; 26:236-238). Applicants respectfully traverse the rejection. Claims 36 and 37 have been canceled, rendering the rejection moot with respect to these claims.

"[F]or anticipation under 35 U.S.C. 102, the reference must teach *every aspect* of the claimed invention either explicitly or impliedly." M.P.E.P. §706.02 (emphasis added). Applicants respectfully submit that Rizzi et al. fail to teach every aspect of the presently claimed invention (e.g., claims 35-40).

Independent claims 35-38 each recite *Staphylococcus aureus* nicotinamide adenine dinucleotide synthetase. In contrast, Rizzi et al. discloses *Bacillus subtilis* nicotinamide adenine dinucleotide synthetase. The present specification discloses that *S. aureus* NAD synthetase (SEQ ID NO:1) has a different amino acid sequence than *B. subtilis* NAD synthetase (SEQ ID NO:2) as illustrated, for example, in Figure 9 and the sequence listings. Moreover, the present specification discloses that crystals of *S. aureus* NAD synthetase differ from crystals of *B. subtilis* NAD synthetase as illustrated, for example, in Figure 7, Figure 8 (e.g., r.m.s. deviation between the C α carbons is 1.19Å), and Figure 10.

Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §102(b).

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*Page 14 of 15***Information Disclosure Statement**

Applicants thanks the Examiner for considering and initialing the documents cited on the 1449 forms submitted by Applicants with an Information Disclosure Statement mailed on December 21, 2001. However, on one of the 1449 forms (page 3 of 5, Exhibit A), the Examiner only initialed the first listed document. For the Examiner's convenience, Applicants are submitting herewith a clean copy of the 1449 form (page 3 of 5, Exhibit B). Consideration of each of the documents listed on the attached 1449 form (Exhibit B) is respectfully requested. Pursuant to the provisions of M.P.E.P. §609, Applicants further request that a copy of the 1449 form, marked as being considered and initialed by the Examiner, be returned with the next Official Communication.

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Summary

It is respectfully submitted that all the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for

Benson et al.

By

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CERTIFICATE UNDER 37 CFR §1.8:

The undersigned hereby certifies that this paper is being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Assistant Commissioner for Patents, Washington, D.C. 20231, on this 30th day of JANUARY, 2003, at 12:42 pm (Central Time).

By:

Name: SAM HER

**APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS
INCLUDING NOTATIONS TO INDICATE CHANGES MADE**

Serial No.: 09/772,598

Docket No.: 6315.N

Amendments to the following are indicated by double underlining what has been added and bracketing what has been deleted. Additionally, all amendments have been indicated by the use of bold font.

In the Specification

Please delete the paragraph beginning at page 10, immediately following line 4 (Table 3).

Please insert the following new paragraph at page 10, immediately following line 4 (Table 3).

Molecule #1	LEU 47	LEU 83	GLU 165	LEU 214
	GLY 48	PHE 132	PHE 170	HIS 260
	ILE 49	ASN 136	TYR 171	LYS 261
	SER 50	ARG 140	THR 172	TYR 266
	SER 55	ARG 142	LYS 173	
	VAL 81	THR 160	ASP 176	
Molecule #2	TYR 1035	PHE 1147	SER 1151	ASP 1180

Please delete the paragraph beginning at page 10, immediately following line 7 (Table 4).

Please insert the following new paragraph at page 10, immediately following line 7 (Table 4).

Molecule #1	LEU 47	GLN 88	GLU 165	GLU 215
	GLY 48	VAL 94	GLY 169	LEU 221
	ILE 49	ILE 111	PHE 170	ASP 223
	SER 50	PHE 132	TYR 171	ALA 226

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	GLY 51	GLY 135	THR 172	TYR 231
	GLY 52	ASN 136	LYS 173	ILE 256
	GLN 53	ALA 139	TYR 174	ARG 257
	ASP 54	ARG 140	GLY 175	ASN 258
	SER 55	ARG 142	ASP 176	ALA 259
	THR 56	GLN 146	GLY 177	HIS 260
	VAL 81	VAL 158	LYS 189	LYS 261
	LYS 82	GLY 159	THR 211	ALA 265
	LEU 83	THR 160	ALA 212	TYR 266
	PRO 84	ASP 161	ASP 213	TRP 271
	TYR 85	HIS 162	LEU 214	
Molecule #2	TYR 1035	GLN 1146	SER 1151	ALA 1179
	HIS 1039	PHE 1147	GLY 1155	ASP 1180
	PHE 1041	SER 1148	ILE 1156	ILE 1181
	ILE 1042	ALA 1150	VAL 1157	

Please delete the paragraph beginning at page 11, immediately following line 2 (Table 5).

Please insert the following new paragraph at page 11, immediately following line 2 (Table 5).

Molecule #1	VAL 46	VAL 94	THR 160	ASP 217
	LEU 47	GLU 95	ASP 161	LYS 218
	GLY 48	ALA 97	HIS 162	LEU 221
	ILE 49	LEU 98	ALA 164	PRO 222

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SER 50	ILE 101	GLU 165	ASP 223
GLY 51	VAL 107	ASN 166	GLU 224
GLY 52	THR 108	THR 168	ASP 225
GLN 53	VAL 109	GLY 169	ALA 226
ASP 54	ASN 110	PHE 170	LEU 227
SER 55	ILE 111	TYR 171	TYR 231
THR 56	THR 130	THR 172	HIS 254
LEU 57	ASP 131	LYS 173	TYR 255
VAL 58	PHE 132	TYR 174	ILE 256
GLY 59	GLN 133	GLY 175	ARG 257
PHE 78	LYS 134	ASP 176	ASN 258
ILE 79	GLY 135	GLY 177	ALA 259
ALA 80	ASN 136	ALA 178	HIS 260
VAL 81	GLU 137	ALA 179	LYS 261
LYS 82	LYS 138	ILE 184	ARG 262
LEU 83	ALA 139	LYS 189	GLU 263
PRO 84	ARG 140	LYS 208	LEU 264
TYR 85	GLU 141	THR 209	ALA 265
GLY 86	ARG 142	PRO 210	TYR 266
VAL 87	MET 143	THR 211	THR 267
GLN 88	VAL 145	ALA 212	THR 270
LYS 89	GLN 146	ASP 213	TRP 271
ASP 90	VAL 157	LEU 214	PRO 272
ALA 91	VAL 158	GLU 215	

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	GLU 93	GLY 159	ASP 216	
Molecule #2	PHE 1031	LEU 1045	ALA 1150	GLY 1159
	TYR 1035	VAL 1046	SER 1151	ALA 1178
	VAL 1036	MET 1143	ASN 1152	ALA 1179
	SER 1038	LYS 1144	ARG 1153	ASP 1180
	HIS 1039	VAL 1145	GLN 1154	ILE 1181
	SER 1040	GLN 1146	GLY 1155	ALA 1182
	PHE 1041	PHE 1147	ILE 1156	
	ILE 1042	SER 1148	VAL 1157	
	SER 1044	ILE 1149	VAL 1158	

The paragraph beginning at page 25, line 22, has been amended as follows:

The structure coordinates set forth in Table 1 can be used to aid in obtaining structural information about another crystallized molecule or molecular complex. A "molecular complex" means a protein in covalent or non-covalent association with a chemical entity or compound. The method of the invention allows determination of at least a portion of the three-dimensional structure of molecules or molecular complexes which contain one or more structural features that are similar to structural features of *S. aureus* NadE. These molecules are referred to herein as "structurally homologous" to *S. aureus* NadE. Similar structural features can include, for example, regions of amino acid identity, conserved active site or binding site motifs, and similarly arranged secondary structural elements (e.g., α helices and β sheets). Optionally, structural homology is determined by aligning the residues of the two amino acid sequences to optimize the number of identical amino acids along the lengths of their sequences; gaps in either or both sequences are permitted in making the alignment in order to optimize the number of identical amino acids, although the amino acids in each sequence must nonetheless remain in

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their proper order. Preferably, two amino acid sequences are compared using the Blastp program, version 2.0.9, of the BLAST 2 search algorithm, as described by Tatusova et al., FEMS Microbiol Lett 174, 247-50 (1999), and available from the world wide web at [<http://www.jncbi.nlm.nih.gov/gorf/bl2.html>]. Preferably, the default values for all BLAST 2 search parameters are used, including matrix = BLOSUM62; open gap penalty = 11, extension gap penalty = 1, gap x_dropoff = 50, expect = 10, wordsize = 3, and filter on. In the comparison of two amino acid sequences using the BLAST search algorithm, structural similarity is referred to as "identity." Preferably, a structurally homologous molecule is a protein that has an amino acid sequence sharing at least 65% identity with the amino acid sequence of *S. aureus* NadE (SEQ ID NO: 1). More preferably, a protein that is structurally homologous to *S. aureus* NadE includes at least one contiguous stretch of at least 50 amino acids that shares at least 80% amino acid sequence identity with the analogous portion of *S. aureus* NadE. Methods for generating structural information about the structurally homologous molecule or molecular complex are well-known and include, for example, molecular replacement techniques.

The paragraph beginning at page 44, line 24, has been amended as follows:

The resolution and quality of the anomalous and dispersive signals were poor making data interpretation difficult. A second data set collected on a selenomethionine incorporated NadE crystal grown in the presence of N³AD was also very mosaic suggesting a fundamental problem with the selenomethionine crystals and/or the cryogenic conditions used to preserve the crystals. However, the data was of sufficient quality at 2.7Å to begin to identify heavy atom positions. Both anomalous and dispersive difference Patterson maps revealed the presence of at least four strong heavy atom peaks (Figures 2-3). A total of eight sites were identified using automated Patterson interpretation methods in SHELX (Sheldrick et al., Acta Cryst., B51:423-31 (1995)). There are [~~five~~]four methionines in each molecule of NadE excluding the N-terminal methionine. Therefore, the eight heavy atom positions would be consistent with the presence of two molecules in the asymmetric unit. Phasing with these eight sites led to electron density

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maps that were difficult to interpret suggesting that the positions of the heavy atom sites might be incorrect except for the fact that these sites were completely consistent with the Patterson maps. Methionine positions from the initial molecular replacement solutions described above using the NadE dimer from *Bacillus subtilis* were also consistent with the peaks in the Patterson maps making the difficulty in refinement and the low quality electron maps even more puzzling.

In the Claims

For convenience, all pending claims are shown below.

35. (Amended) A method for crystallizing [an] *Staphylococcus aureus* nicotinamide adenine dinucleotide (*S. aureus* NAD) synthetase [molecule or molecular complex] comprising: providing purified *S. aureus* NAD synthetase at a concentration of about 1 mg/ml to about 50 mg/ml; and

crystallizing *S. aureus* NAD synthetase from a solution comprising about 5% by weight to about 50% by weight polyethylene glycol (PEG) and about 0% by weight to about 20% by weight dimethyl sulfoxide (DMSO).

38. (Amended) A crystal of *Staphylococcus aureus* nicotinamide adenine dinucleotide (*S. aureus* NAD) synthetase.

39. The crystal of claim 38 having the trigonal space group symmetry $P2_1$.

40. The crystal of claim 38 comprising a unit cell having dimensions of a, b, and c; wherein a is about 40Å to about 60Å, b is about 90Å to about 120Å, and c is about 80Å to about 110Å; and wherein $\alpha = \gamma = 90^\circ$ and β is about 80° to about 120°.

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41. The crystal of claim 38 comprising atoms arranged in a spatial relationship represented by the structure coordinates listed in Table 1.
42. The crystal of claim 38 having amino acid sequence SEQ ID NO:1.
43. The crystal of claim 38 having amino acid sequence SEQ ID NO:1, with the proviso that at least one methionine is replaced with selenomethionine.